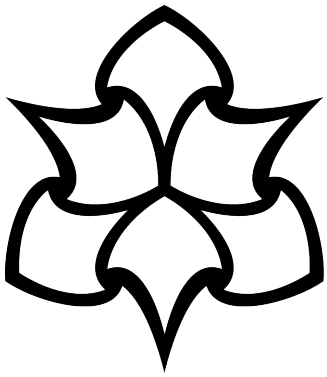

Segregating the Distinct Effects of Sedentary Behavior and Physical Activity on Older Adults' Cardiovascular Profile: Part 2—Isotemporal Substitution Approach

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Background: The aim of the study was to provide an isotemporal substitution model to predict how changes in physical behavior may affect the cardiovascular parameters (CVPs) of older adults. **Methods**: Participants wore a thigh-mounted accelerometer for 7 days. Phenotype of the carotid, brachial, and popliteal artery was conducted using ultrasound. Isotemporal substitution was used to simulate the degree to which replacing 1 hour of physical behavior with another would affect CVP. **Results**: Substitution of sedentary behavior with Standing and sporadic moderate- to vigorous-intensity physical activity (MVPA accumulated in bouts <10 min) would reduce resting heart rate [−6.20 beats per minute (−12.1 to −0.22) and −3.72 beats per minute (−7.01 to −0.44), respectively]. Substitution of sedentary behavior with light-intensity physical activity would reduce carotid artery diameter [−0.54 mm (−1.00 to −0.07)]. Substitution of Standing with sporadic MVPA would increase popliteal artery diameter [1.31 mm (0.11 to 2.51)]. **Conclusions**: Our modeling suggests that an accumulation of MVPA bouts that are shorter than the recommended 10-minute minimum may still improve CVP, with lower intensity physical activity also influencing CVP. Our findings are a promising avenue for lifestyle interventions in older adults to reduce the aging effects on CVP for those who cannot engage or sustain sufficient MVPA.

Keywords: accelerometry, sitting/standing, epidemiology, gerontology

It is becoming evident that sedentary behavior (SB) affects a number of physiological parameters independent of the amount of moderate- to vigorous-intensity physical activity (MVPA) engagement.[1,2] With time being finite within a day (ie, 24-h end point), engagement in one physical behavior (PB)[3] will offset the amount of time that can be spent performing another. Standard regression modeling fails to recognize the time constraints, and therefore, the use of multiple measures of PB within a regression model will not account for the time that is displaced by engaging is a specific bout of PB.

Isotemporal substitution regression models recognize that time is finite by including a measure of total PB [eg, sum of waking hours SB and physical activity (PA)], which is kept constant and therefore provides the opportunity to substitute one PB for another, thereby reflecting the realities of daily life.[4] Rather than prediction, per se, isotemporal substitution reflects the decisions people have made (eg, prolonged SB) and offers an extrapolation of what would happen should they decided to do something different (eg, MVPA). Therefore, this analysis may be more advantageous to public health PB action plans, as it clearly illustrates what will happen to markers of health if habitual PB levels and/or patterns are changed. In older adult populations, isotemporal substitution has mainly been used to assess the effect on cardiometabolic[5–7] rather than cardiovascular parameters (CVPs).[8] However, in the one study to date, to the authors' knowledge, in which CVPs have been assessed, it has demonstrated promising results, for instance, suggesting the substitution of SB with light-intensity PA (LIPA) would reduce the relative risk of cardiovascular disease (CVD) prevalence within older adult cohorts.[8] LIPA is a promising intervention to reduce SB for older adult populations as it can arguably prove to be easier (in comparison with MVPA) to comply with and be accumulated to consist the greater majority of a 24-hour simplex.[9]

Moreover, the 10-minute minimum threshold for an MVPA bout ($_{10}$MVPA), highlighted in the PA guidelines,[10] to show clinically beneficial outcomes, has not been examined using isotemporal substitution. If sporadic MVPA (sMVPA, accumulated in bouts of less than 10 continuous minutes) has beneficial effects on cardiovascular health, this alternative mode of accumulating MVPA would likely allow older adults to improve their health within their physical capacities and maintain this PB profile in the long term. Therefore, the objective of part 2 of this series was to simulate the degree to which the substitution of SB and lower intensity PA with MVPA would have positive effects on cardiovascular health markers and vice versa in older adults. The aim was to provide a time-constrained, alternative to bivariate/multivariate regression modeling, tool to predict how changes in PB may affect the cardiovascular health of older adults. It was hypothesized that substituting SB with any intensity of PA would improve CVPs and that substituting a PB with a higher intensity would improve cardiovascular profile. It was also hypothesized that substituting SB with $_{10}$MVPA would have a greater effect on CVPs than seen with sMVPA substitutions.

Methods

Ninety-three older participants [73.8 (6.22) y, 60–89 y, 55% female; Table 1], who did not suffer from an untreated CVD,

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Table 1 Participant Demographics

Variable	Mean (SD)
Age, y	73.8 (6.22)
Height, m	1.65 (0.08)
Mass, kg	75.9 (13.1)
BMI, kg/m^2	27.9 (4.71)
Primary CVD medication,[a] %	48.0
(In)direct CVD medication,[b] %	59.0
Hydration, %	50.6 (7.15)
SB, h/d	9.68 (1.30)
Standing, h/d	1.10 (0.40)
LIPA, h/d	1.95 (0.60)
sMVPA, h/d	2.58 (0.66)
$_{10}$MVPA, h/d	0.08 (0.18)[c]
Total PB, h/d	15.4 (4.77)[c]

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; LIPA, light-intensity physical activity; $_{10}$MVPA, 10-minute moderate- to vigorous-intensity physical activity (accumulated in bouts ≥10 min); PB, physical behavior; SB, sedentary behavior; sMVPA, sporadic moderate- to vigorous-intensity physical activity (accumulated in bouts <10 min).

[a]Participants are currently prescribed an amount of medication that reduces the risk or treats CVD (ie, statins, warfarin).

[b]Participants are currently prescribed a medication that may affect the cardiovascular system either directly or as a side effect.

[c]Data are presented as median (interquartile range).

had not sustained a PB limiting injury within the last 3 months, were independently mobile, and deemed generally healthy, were recruited for the study. Participant approval for study inclusion was provided with a written informed consent, and the study was granted approval by the Manchester Metropolitan University Ethics Subcommittee. Participants visited the laboratory on 2 occasions separated by at least 7 days.

First Laboratory Visit

The methods follow that of part 1 of the current series of papers. In brief, participant demographics (Table 1) were collected during the first laboratory visit. Medication use was provided through hard copies of current prescriptions, with hard copy medication later categorized as primarily used to target CVD or could indirectly target CVD. This information is reported as primary CVD medication (number of drugs primarily targeting CVD) or (in)direct CVD medication (sum of primary CVD medication and drugs that may indirectly affect CVD). Participants were fitted with a commercially available, dominant leg, thigh-mounted (anterior aspect, at 50% of greater trochanter to femoral condyle distance) triaxial accelerometer (GENEA, GENEActiv Original; Activinsights Ltd, Kimbolton, UK) using a waterproof adhesive patch (Tegaderm Film; 3M, North Ryde, Australia), for 7 consecutive free-living days. Residual G (Residual G = $\sqrt{[(\mathrm{SD}\ x)^2 + (\mathrm{SD}\ y)^2 + (\mathrm{SD}\ z)^2]}$), adapted from our previous work on older adults total movement,[11] was used to analyze the 10-second epoch (60.0 Hz) GENEA data and termed The Cheshire Algorithm for Sedentarism. The Cheshire Algorithm for Sedentarism was developed using cutoff points developed in our laboratory calibrated against the expired gas samples of a subsample of 20 older adults for 10 PBs. SB was recognized as any seated or reclined posture, using the GENEA axes orientation, similar to that of the "sedentary sphere,"[12] whereas Standing was recognized as any standing posture that had a Residual G[11] value below the SB–LIPA cutoff point of 0.057 G [representing 1.50 metabolic equivalent tasks (METs)]. Remaining standing postures were then classified into LIPA or MVPA dependent on whether they met the LIPA–MVPA cutoff point of 0.216 G (representing 3.00 METs). MVPA was categorized as sMVPA if bouts were less than 10 continuous minutes in duration or $_{10}$MVPA if bouts were greater than or equal to 10 continuous minutes in duration. One MET was equal to the resting metabolic rate (while seated) of the participants to account for individual differences in physical fitness. There was a strong association between Residual G and METs ($r^2 = .89$, $P < .01$). Postural identification showed a perfect agreement with known time spent performing SB and PA [Cohen's $\kappa = 1.00$; 95% confidence interval (CI), 1.0 to 1.0; $P < .01$]. Residual G cutoff points and MET thresholds had a strong agreement for PB intensity classification (Cohen's $\kappa = 0.81$; 95% CI, 0.49 to 1.31; $P < .01$). Sleeping hours data were collected through a self-reported sleep diary (wake-up time, lights-off go to sleep time, and naps not included) throughout the monitoring week.

Second Laboratory Visit

Upon arrival of the second laboratory visit in a fasted and hydrated state, a standardized meal (30.0 g of carbohydrate, 24.0 g of protein, and 8.0 g of fat) was provided before continuation with the testing session.

Participants were fitted with a 3-lead electrocardiogram, as described in part 1 of the current series, and rested in the supine position for 15 minutes to minimize the impact of orthostatic change.[13] Room temperature (22.0°C) and light intensity (20.0 lm·ft^2) were kept constant throughout the testing. Hydration status, represented as a percentage of total body mass, was determined using right wrist to right ankle bioelectrical impedance (Bodystat 1500; Bodystat, Douglas, UK).

Echo Doppler ultrasound (model AU5; Esaote, Genova, Italy) using a 7.50-MHz broadband linear array transducer was used to perform vascular assessments (angle of insonation: 60.0°, brightness gain: 75.0, Doppler gain: 49.0, color flow mode gain: 47.0, depth of penetration: 49.3 mm, and depth of focus: 27.0–31.0). Live streamings were collected on a Hewlett-Packard computer running video capture software through an analog to digital converter (Pinnacle; Corel Inc, Ottawa, Canada) at 25.0 Hz. Left common carotid artery and right brachial artery assessments were performed in the supine position, whereas left popliteal artery assessments were performed in the prone position. Baseline systemic peak blood velocity, intima-media thickness (IMT), artery diameter, calculation of shear rate, and resistance index (carotid artery only) measures were collected over 10 cardiac cycles for all 3 arteries (definitions provided in part 1 of this series). All measurements occurred within a 10-mm region of interest, 10-mm distal of the carotid bulb in the anterior longitudinal (AL) and posterior longitudinal plane, 10-mm distal of the superior medial genicular bifurcation of the popliteal artery, and 65.0% of upper arm length (acromion process to lateral radial head) distal of the glenohumeral joint for the brachial artery.[13–17] These CVPs were selected due to the exploratory nature of this study in an attempt to distinguish any limb-specific associations between PB and CVPs.

Offline analyses of diameter measures for all arteries were performed using Brachial Analyzer (Medical Imaging Application LLC, Coralville, Iowa), and IMT measures of all arteries were performed with Carotid Analyzer (Medical Imaging Application LLC). Data were R-gated to ensure artery diameter, and IMT were

measured during the diastolic phase only. Frame-to-frame measurements were filtered from final analysis if they did not use 70.0% of the region of interest and/or were more than 1 SD from the mean artery diameter or IMT. All automated processes were assessed for error by one researcher. Intraday coefficients for variation (CV) ranged from 2.34% to 4.97%, whereas interday CV ranged from 1.57% to 5.33% for artery diameter. Intraday CV ranged from 3.04% to 7.04%, whereas interday CV ranged from 1.45% to 11.3% for IMT. Blood velocity interday and intraday CV were below 20.0% for all arteries. Shear rate interday and intraday CV were below 16.0% for all arteries. Carotid resistance index interday and intraday CV were below 12.0%. All CV measures indicated that there was sufficient sensitivity to detect changes in cardiovascular health based on observed changes in these variables following PB interventions.[18–20]

Statistical Analyses

SPSS version 22 (IBM, New York, NY) was used for statistical analyses. Pearson correlation was used to assess multicollinearity between PB parameters and total PB; no adjustment was made to the data if multicollinearity was present. Isotemporal substitution regression modeling (forced entry) was implemented to examine the impact of 1 hour of PB substitution.[4] Isotemporal substitution modeling is performed by removing one PB (hereafter referred to as the substituted PB) from the regression model [ie, substituted SB model = Intercept + ($\beta 1 \times$ Standing) + ($\beta 2 \times$ LIPA) + ($\beta 3 \times$ sMVPA) + ($\beta 4 \times {}_{10}$MVPA) + ($\beta 5 \times$ Total PB) + Covariates + Error]. Significant PB predictors within the isotemporal substitution model illustrate that replacing 1 hour of the substituted PB (as data are measured in hours per day) with the significant PB would have an effect on the respective CVP [magnitude of unit change illustrated by beta coefficient and 95% CI(s)]. Including total PB at the end of the isotemporal substitution model represents the time-constrained hours within a waking hours day, which standard linear regression modeling does not account for. Isotemporal substitution models were conducted without (model 1) and with (model 2) adjustment for covariates to determine how hydration status and medication affect the relationship between PB and cardiovascular profile. Hydration status was used as a covariate as it has been shown to affect artery diameter,[21] whereas medication use was used as a covariate as it has been shown to effect CVPs.[22–24] Hydration, primary CVD medication, and (in)direct CVD medication were used for covariate adjustment where preceding bivariate linear regressions had shown that they were significantly associated with specific CVPs. Cardiovascular data were natural log transformed if they violated normal distribution. Data are presented as beta coefficient (95% CI) unless otherwise stated.

Results

Isotemporal Substitution

Isotemporal substitution showed that changes in PB levels would significantly affect 3 out of the 19 assessed CVPs (Online Supplementary Material), these being resting heart rate, carotid AL artery diameter, and popliteal artery diameter. The significant substitutions are shown in Figure 1.

Substitution of SB with Standing and sMVPA was suggested to reduce resting heart rate [Figure 1; −6.20 beats per minute (−12.1 to −0.22) and −3.72 beats per minute (−7.01 to −0.44), respectively], which is clinically relevant as a 5 beats per minute increase in resting heart rate increases the risk of cardiovascular mortality by 3% (2.0% to 4.0%).[25] After the substitution of SB with LIPA, carotid AL artery diameter was predicted to reduce [Figure 1; −0.54 mm (−1.00 to −0.07)] and vice versa [Figure 1; 0.54 mm (0.08 to 1.00)], which is clinically relevant as a 0.78-mm increase is associated with a 2.1 (1.3 to 3.3) hazard ratio risk of all-cause mortality.[26] Substitution of Standing with sMVPA [Figure 1; 1.31 mm (0.11 to 2.51)] would

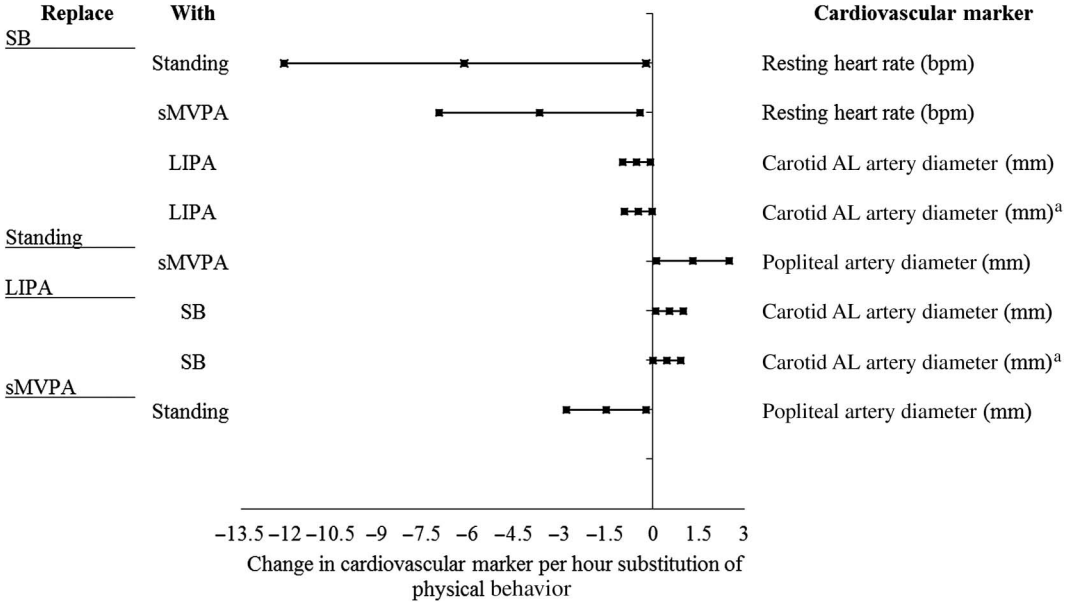

Figure 1 — Significant physical behavior isotemporal substitutions and their impact on cardiovascular parameters. Markers indicate (left to right) −95% CI, beta coefficient, and +95% CI. SB indicates sedentary behavior; LIPA, light-intensity physical activity; sMVPA, sporadic moderate- to vigorous-intensity physical activity (accumulated in bouts <10 min); AL, anterior longitudinal plane; bpm, beats per minute; CI, confidence interval; CVD, cardiovascular disease. [a]Normalized for primary CVD medication.

increase popliteal artery diameter and vice versa [Figure 1; −1.52 mm (−2.83 to −0.22)]. This result is clinically relevant as an 8-week interval training program increased popliteal artery diameter by 0.14 mm per hour of training[27] as well as the popliteal artery diameter of healthy controls being 0.6 mm ($P = .11$) larger than those with coronary artery disease (males aged 40–70 y).[28]

Within model 2, the results for all cardiovascular variables remained the same after covariate adjustment suggesting that covariates had no effect on the relationship between PB and cardiovascular profile.

Multicollinearity

The largest correlation coefficient within the multicollinearity matrix was between SB and LIPA, sMVPA (both $r = -.69$), while the remaining variables only had weak correlations suggesting low influence of collinearity on the results (Table 2).

Discussion

The objective of this study was to determine whether the substitution of SB and lower intensity PA with MVPA would have positive effects on cardiovascular health and vice versa, in older adults. The aim was to provide a time-constrained tool, alternative to bivariate/multivariate regression modeling, to simulate how changes in PB would affect the cardiovascular profile of older adults. It was hypothesized that substituting SB with any intensity of PA would improve CVPs and that substituting a PB with a higher intensity would improve cardiovascular profile. It was also hypothesized that substituting SB with $_{10}$MVPA would have a greater effect on CVPs than seen with sMVPA substitutions.

Heart rate is controlled by the central nervous system, which is compromised of the sympathetic and parasympathetic pathways. The simulation of the replacement of SB with Standing or sMVPA suggested that it would reduce resting heart rate. Physiologically, this could be achieved through improved baroreceptor function, which naturally declines with age.[29] Given that 6 weeks of yoga [consisting mainly of static postures (and breathing exercises)] has been reported to improve high-frequency baroreceptor sensitivity and to reduce resting heart rate in older adults (whereas prolonged aerobic training did not),[30] a similar effect may be at play in the Standing PB within our current modeling. High-frequency baroreceptors represent the sympathetic nervous system, suggesting that vasoconstriction response was improved to counteract the natural fall in blood pressure with standing activities.[31] Subsequently, increased vasoconstriction would increase venous return and stroke volume, which would result in the need for a lower heart rate to maintain resting cardiac output. On the other hand, the modeling of reduction in heart rate through increased sMVPA may be achieved via improvements in the parasympathetic pathway. Interval training consisting of nine 5-minute repeated bouts at 65% of maximum heart rate (MVPA) over 14 weeks improved markers of parasympathetic activity [PNN50 (percentage of successive normal sinus heart rate variability intervals >50.0 ms) and RMSSD (root mean square of the successive normal sinus RR interval difference)] and subsequently decreased 24-hour mean heart rate within older adults.[32] Therefore, the simulations from real data in our current study suggest that reducing SB with PA, such as Standing (arguably easy to accumulate, due to limiting the common socioeconomic-volition barriers to structured exercise normally reported in older persons[33]), could yield health benefits. However, engagement in MVPA is also important, as it would appear that different pathways are targeted by the 2 distinct PA intensities.

The reduction in resting heart rate may also be a result of vascular remodeling within compliant blood vessels, such as the carotid and popliteal arteries, but not the stiffer brachial artery. With aging, artery diameter increases as elastin stiffness decreases causing the load bearing to shift to collagen fibers within the vascular smooth muscle.[34] This structural change may not be due solely to aging but also due to increased SB, as the substitution of LIPA with SB suggested it would increase carotid AL artery diameter in our modeling. The opposite association was shown when the reverse substitution between SB and LIPA was made. These inferences are in line with previous older adult research that found an increase and decrease in carotid–femoral pulse wave velocity with increased engagement in LIPA and SB, respectively.[35]

The increase in arterial stiffness with aging is also a determinant for the fall in orthostatic blood pressure, which begins before baroreceptor mediated reflexes.[36] Orthostatic posture increases lower limb blood pressure, which subsequently leads to an increase in total peripheral resistance and declined cardiac output. With the substitution of Standing with sMVPA, it was suggested that popliteal artery diameter would increase. This, in line with Poiseuille's law of flow, would decrease local blood pressure and thus total peripheral resistance. However, sMVPA engagement would also acutely increase blood flow.[37] Blood flow declines with age in the legs due to increased sympathetic activity,[38] the latter which could increase total peripheral resistance. Training interventions within physically inactive have shown that the acute vascular responses to interval training (MVPA bouts <10 min, representative of sMVPA) stimulate baroreceptor activity[32] and increase artery diameter,[27] subsequently leading to improved popliteal endothelial function and distensibility.[39] Overall, our results suggest a potential for older adults who cannot/choose not to sustain MVPA for 10 continuous minutes to still attain positive vascular adaptations (reduced resting heart rate and increased popliteal artery diameter). This is relevant given the sample population averaged less than 1 $_{10}$MVPA bout per day [0.28 (0.71) *n* per day] and only 34.2 (81.6) minutes per week of $_{10}$MVPA, suggesting the majority of the study population could not/chose not to sustain MVPA for 10 continuous minutes (see part 1 of this series).

Table 2 Collinearity Statistics for PB Parameters

	SB	Standing	LIPA	sMVPA	$_{10}$MVPA	Total PB
SB	–	−.58***	−.69***	−.69***	−.23*	.32**
Standing		-	.64***	.35**	.01	.24*
LIPA			-	.45***	−.02	.13
sMVPA				–	.19	.23*
$_{10}$MVPA					–	.05

Note. Data are Pearson correlations.

Abbreviations: LIPA, light-intensity physical activity; $_{10}$MVPA, 10-minute moderate- to vigorous-intensity physical activity (accumulated in bouts ≥10 min); PB, physical behavior; SB, sedentary behavior; sMVPA, sporadic moderate- to vigorous-intensity physical activity (accumulated in bouts <10 min).

*$P \le .05$. **$P \le .01$. ***$P \le .001$.

Conclusion

Our isotemporal substitution modeling suggests that an accumulation of MVPA bouts that are shorter than the recommended 10-minute minimum would improve CVPs (including resting heart rate and popliteal artery diameter), with lower intensity PA also influencing CVPs. Our findings are therefore a promising avenue

for lifestyle interventions in older adults to reduce the aging effects on cardiovascular health, especially those end users who cannot engage or sustain sufficient MVPA to be classed as physically active. The replacement of SB with PA influenced 2 of the 19 CVPs (resting heart rate and carotid AL artery diameter), whereas the replacement of sMVPA with a lower intensity PB influenced 1 CVP (popliteal artery diameter). Our findings suggest that the reduction of SB is just as important as the need to be physically active for older adults.

Finally, the current study illustrates the usefulness of isotemporal substitution modeling in simulating the different effects (and/or physiological pathways) that a PB outcome of interest may have on a unique (or a set of) CVP(s), dependent on the PB it is displacing. This is the first study, to the authors' knowledge, to demonstrate changes in cardiovascular phenotype within an isotemporal substitution model for an older adult cohort using objective measures of PB and CVPs.

Intervention studies are needed to determine the time course of the suggested temporal changes shown in isotemporal substitution modeling in older adult populations.

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